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Niraparib Maintenance Therapy in Patients With Recurrent Ovarian Cancer After a Partial Response to the Last Platinum-Based Chemotherapy in the ENGOT-OV16/NOVA Trial

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abstract

PURPOSE In the ENGOT-OV16/NOVA trial (ClinicalTrials.gov identifier: NCT01847274), maintenance therapy with niraparib, a poly(ADP-ribose) polymerase inhibitor, prolonged progression-free survival in patients with platinum-sensitive, recurrent ovarian cancer who had a response to their last platinum-based chemotherapy. The objective of the study was to assess the clinical benefit and patient-reported outcomes in patients who had a partial response (PR) and complete response (CR) to their last platinum-based therapy.

PATIENTS AND METHODS A total of 553 patients were enrolled in the trial. Of 203 patients with a germline *BRCA* mutation (g*BRCA*mut), 99 had a PR and 104 had a CR to their last platinum-based therapy; of 350 patients without a confirmed g*BRCA*mut (non–g*BRCA*mut), 173 had a PR and 177 had a CR. Post hoc analyses were carried out to evaluate safety and the risk of progression in these patients according to g*BRCA*mut status and response to their last platinum-based therapy. Ovarian cancer–specific symptoms and quality of life were assessed using the Functional Assessment of Cancer Therapy–Ovarian Symptom Index.

RESULTS Progression-free survival was improved in patients treated with niraparib compared with placebo in both the g*BRCA*mut cohort (PR: hazard ratio [HR], 0.24; 95% CI, 0.131 to 0.441; $P < .0001$; CR: HR, 0.30; 95% CI, 0.160 to 0.546; $P < .0001$) and the non–g*BRCA*mut cohort (PR: HR, 0.35; 95% CI, 0.230 to 0.532; $P < .0001$; CR: HR, 0.58; 95% CI, 0.383 to 0.868; $P = .0082$). The incidence of any-grade and grade 3 or greater adverse events was manageable. No meaningful differences were observed between niraparib and placebo in PR and CR subgroups with respect to patient-reported outcomes.

CONCLUSION Patients achieved clinical benefit from maintenance treatment with niraparib regardless of response to the last platinum-based therapy.

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ASSOCIATED CONTENT

Appendix

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

The majority of women with advanced ovarian cancer will experience recurrence after first-line treatment with platinum-based chemotherapy,[1] and recurrent ovarian cancer is considered incurable.[2] After first-line platinum-based chemotherapy, 70% to 80% of patients with ovarian cancer have platinum-sensitive disease,[1] defined as having a complete or partial response (CR or PR) to platinum-based chemotherapy and no progression of disease within 6 months of the final dose of chemotherapy.[3] In most cases, successive lines of platinum-based therapy lead to the development of platinum resistance,[1] defined as an initial response (CR or PR) to platinum-based chemotherapy with progression less than 6 months after the final dose of chemotherapy.[3]

Maintenance treatment with a poly(ADP-ribose) polymerase (PARP) inhibitor during the chemotherapy-free interval is now recommended as a therapeutic option available to patients with recurrent ovarian cancer.[4,5] Maintenance treatment with PARP inhibitors recently has been shown to prolong the progression-free interval, which allows patients longer times between chemotherapy regimens.[6-8]

The National Comprehensive Cancer Network guidance on maintenance therapy originally recommended consideration of maintenance therapy for patients with a CR, and recurrence therapy was recommended for patients with a PR (and residual tumor mass). In 2017, the National Comprehensive Cancer Network guidelines were updated to include maintenance therapy for patients with a PR as well as those

with a CR. Since 2016, European Society for Medical Oncology treatment guidelines have also recommended maintenance therapy offered to patients with a PR or CR to platinum-based therapy.[4] Although the pivotal phase III ENGOT-OV16/NOVA trial of niraparib maintenance therapy enrolled patients with either a PR or CR to platinum-based chemotherapy,[7] no analyses were performed to determine the effect of response to the last platinum therapy on the efficacy of niraparib. It is important to understand whether maintenance therapy with niraparib is of value in patients with a PR after platinum-based therapy and those with complete tumor responses.

The objective of this analysis was to assess the safety and efficacy of niraparib in patients enrolled in the ENGOT-OV16/NOVA trial on the basis of best response to the last platinum-based therapy. We also present quality-of-life (QoL) measures using data from the Functional Assessment of Cancer Therapy–Ovarian (FACT-O) Symptom Index (FOSI) for patients by best response to the last platinum-based therapy.

PATIENTS AND METHODS

ENGOT-OV16/NOVA (ClinicalTrials.gov identifier: NCT01847274) was a multicenter, double-blind, randomized, placebo-controlled, phase III study that enrolled patients with recurrent ovarian cancer. Patients must have completed at least two previous courses of platinum-containing therapy before random assignment. For the penultimate platinum-based chemotherapy regimen, patients must have had platinum-sensitive disease, defined as achievement of a response (CR or PR) and no progressive disease within 6 months after completion of the last dose of platinum-based chemotherapy. For the last platinum-based chemotherapy regimen, patients must have received a platinum-containing regimen for a minimum of four cycles and achieved a CR or PR. After the last regimen, patients could not have had any measurable lesion greater than 2 cm at the time of study entry.

Patients were assigned to one of two independent cohorts—germline breast cancer susceptibility gene (*BRCA*) mutation (g*BRCA*mut) or non–g*BRCA*mut—on the basis of results

TABLE 1. Patient Characteristics at Baseline by Response to the Last Platinum-Based Chemotherapy

	g*BRCA*mut Cohort (n = 203)		Non–g*BRCA*mut Cohort (n = 350)	
Characteristic	**PR to Last Platinum (n = 99)**	**CR to Last Platinum (n = 104)**	**PR to Last Platinum (n = 173)**	**CR to Last Platinum (n = 177)**
Median (min, max) age, years	60.0 (39, 83)	52.0 (36, 76)	63.0 (33, 83)	63.0 (40, 84)
ECOG performance status				
0	62 (62.6)	77 (74.0)	106 (61.3)	132 (74.6)
1	37 (37.4)	27 (26.0)	67 (38.7)	45 (25.4)
Mean (SD) duration of last platinum-based chemotherapy, months	4.7 (1.95)	4.8 (2.01)	4.7 (1.76)	4.7 (2.09)
Had prior use of bevacizumab	15 (15.2)	35 (33.7)	44 (25.4)	48 (27.1)
Best response to penultimate platinum-based chemotherapy*				
PR	40 (40.4)	17 (16.3)	73 (42.2)	23 (13.0)
CR	58 (58.6)	87 (83.7)	99 (57.2)	152 (85.9)
Time to PD after penultimate platinum-based dose, months				
6 to < 12	44 (44.4)	36 (34.6)	78 (45.1)	56 (31.6)
≥ 12	55 (55.6)	68 (65.4)	95 (54.9)	121 (68.4)
Previous lines of chemotherapy†				
2	46 (46.5)	54 (51.9)	100 (57.8)	132 (74.6)
≥3	52 (52.5)	50 (48.1)	73 (42.2)	44 (24.9)
Previous lines of platinum-based chemotherapy†				
2	53 (53.5)	63 (60.6)	114 (65.9)	147 (83.1)
≥ 3	45 (45.5)	41 (39.4)	59 (34.1)	29 (16.4)

NOTE. Data presented are No. (%) of patients unless otherwise noted.

Abbreviations: CR, complete response; ECOG, Eastern Cooperative Oncology Group; g*BRCA*mut, germline breast cancer susceptibility gene mutation; PD, progressive disease; PR, partial response; SD, standard deviation.

*Data were missing for one patient with a PR to the last platinum-based therapy in the g*BRCA*mut cohort, one patient with a PR to the last platinum-based therapy in the non–g*BRCA*mut cohort, and two patients with a CR to the last platinum-based therapy in the non–g*BRCA*mut cohort.

†One patient with a PR to the last platinum-based therapy in the g*BRCA*mut cohort had only one line of prior chemotherapy, which was platinum based; one patient with a CR to the last platinum-based therapy in the non–g*BRCA*mut cohort had missing data on previous lines of chemotherapy.

from the BRAC*Analysis* test (Myriad Genetics, Salt Lake City, UT) and were randomly assigned 2:1 within each cohort to receive niraparib 300 mg or placebo once daily until progression of disease or death. Random assignment occurred within 8 weeks of the last platinum-based chemotherapy cycle and was stratified within each cohort according to best response (CR or PR) to the last platinum-based regimen, time to progression after completion of the penultimate platinum-based regimen, and prior use of bevacizumab in conjunction with at least one prior chemotherapy.

Analyses

Baseline and demographic characteristics were descriptively summarized by cohort (g*BRCA*mut and non–g*BRCA*mut) and best response (PR or CR) to the last platinum-based therapy. Post hoc efficacy and safety analyses were performed by cohort and best response to the last platinum-based chemotherapy. Progression-free survival (PFS) was defined as the time from treatment random assignment to the earliest date of disease progression or death as a result of any cause. Disease progression was assessed by independent radiologic review and central review by a clinician who was unaware of study group assignments. PFS was summarized using Kaplan-Meier methodology. For each subgroup, the hazard ratio (HR) was estimated along with the two-sided 95% CI using a stratified Cox proportional hazards model and the stratification factors used in random assignment. The incidence of adverse events (AEs) was descriptively summarized by treatment group and best response to the last platinum-based therapy. No inferential statistics were performed.

Patient-Reported Outcomes

The FOSI questionnaire was used to assess ovarian cancer–specific symptoms and QoL. The FOSI is a validated 8-item measure of symptom response to treatment of ovarian cancer on the basis of a subset of questions from the FACT-O questionnaire.[9] Patients report their symptom experience during the past 7 days using a 5-point Likert scale, which ranges from "not at all" (0) to "very much" (4). The FOSI is calculated as the total of eight symptoms: pain, fatigue, nausea, vomiting, bloating, cramping, worry, and QoL. An

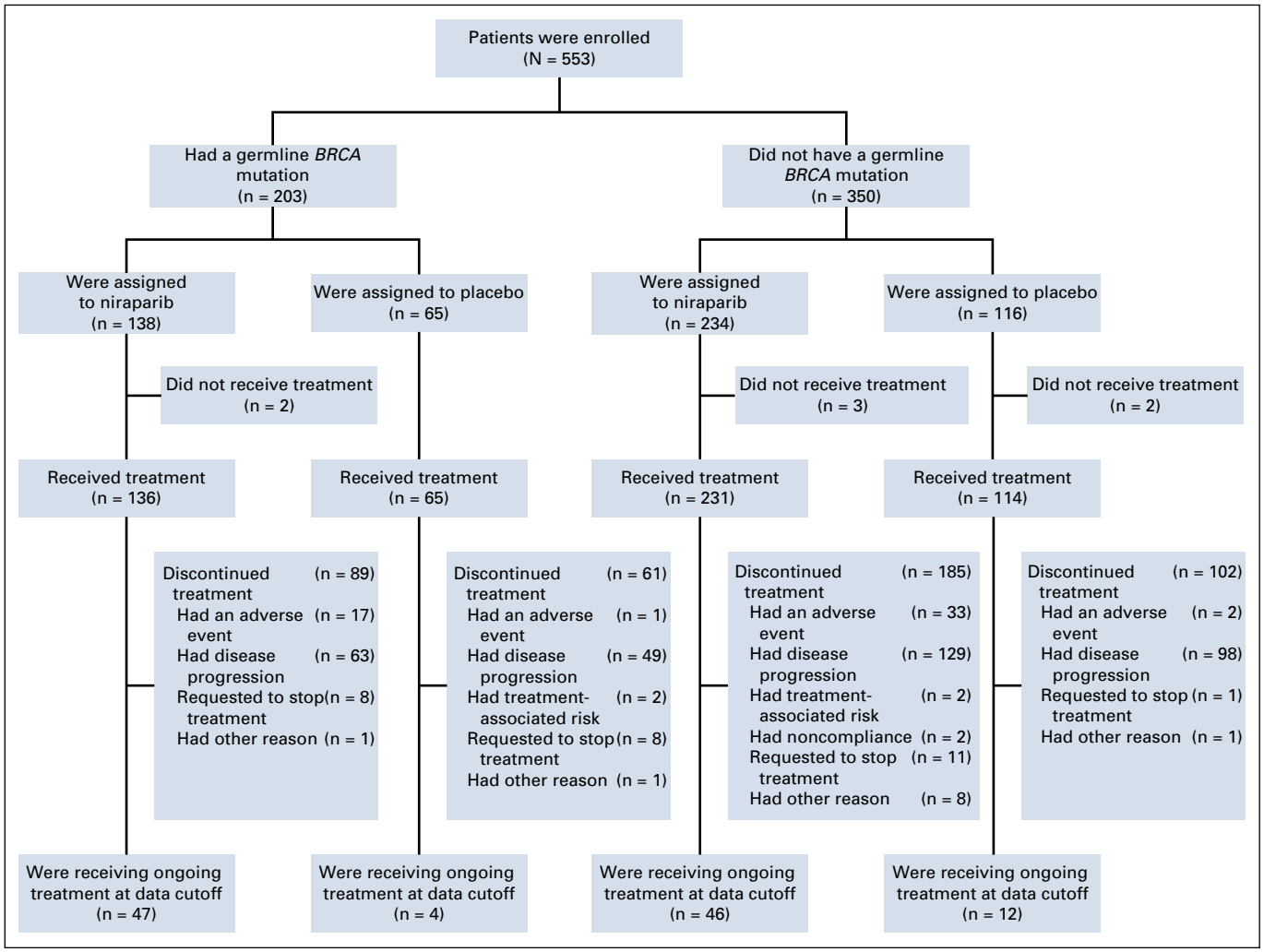

FIG 1. Study enrollment and outcomes. *BRCA*, breast cancer susceptibility gene. Reprinted with permission.[7]

analysis of the change from baseline in overall FOSI score was performed using a mixed model with treatment, visit, subgroup, treatment-by-visit interaction, treatment-by-subgroup interaction, and treatment-by-subgroup-by-visit interaction as fixed effects and patient as a random effect. Analyses of the individual symptom-related questions were also performed. Patients were categorized as symptomatic if their response was 1 or more and as severely symptomatic if their response was 3 or 4. The percentages of patients with any symptom and with severe symptoms were summarized over time by the best response (CR or PR) to the last platinum-based chemotherapy regimen.

RESULTS

Demographics and Baseline Characteristics

A total of 553 patients were enrolled and randomly assigned to treatment in the ENGOT-OV16/NOVA trial: 203 in the g*BRCA*mut cohort and 350 in the non–g*BRCA*mut cohort (Table 1; Fig 1). Topline results have been previously reported.[7] In both cohorts, 49% of patients entered the study with a PR to their last platinum-based chemotherapy (Table 1). In the g*BRCA*mut cohort, patients with a CR tended to be younger than those with a PR; no difference in age was noted between patients with a CR and PR in the non–g*BRCA*mut cohort. The mean time from completion of the last dose of platinum-based chemotherapy and random assignment was 43.2 days for patients with a CR and was 43.8 days for patients with a PR. Within each cohort, duration of the last platinum-based treatment before random assignment was similar among patients with PRs and CRs. At trial entry, patients with a CR to their last platinum-based chemotherapy tended to have a better performance status (Eastern Cooperative Oncology Group performance status of 0 *v* 1) than patients with a PR to their last platinum-based chemotherapy. Patients with a PR to their last platinum-based therapy had, on average, received more lines of prior treatment than those with a CR to their last platinum-based therapy.

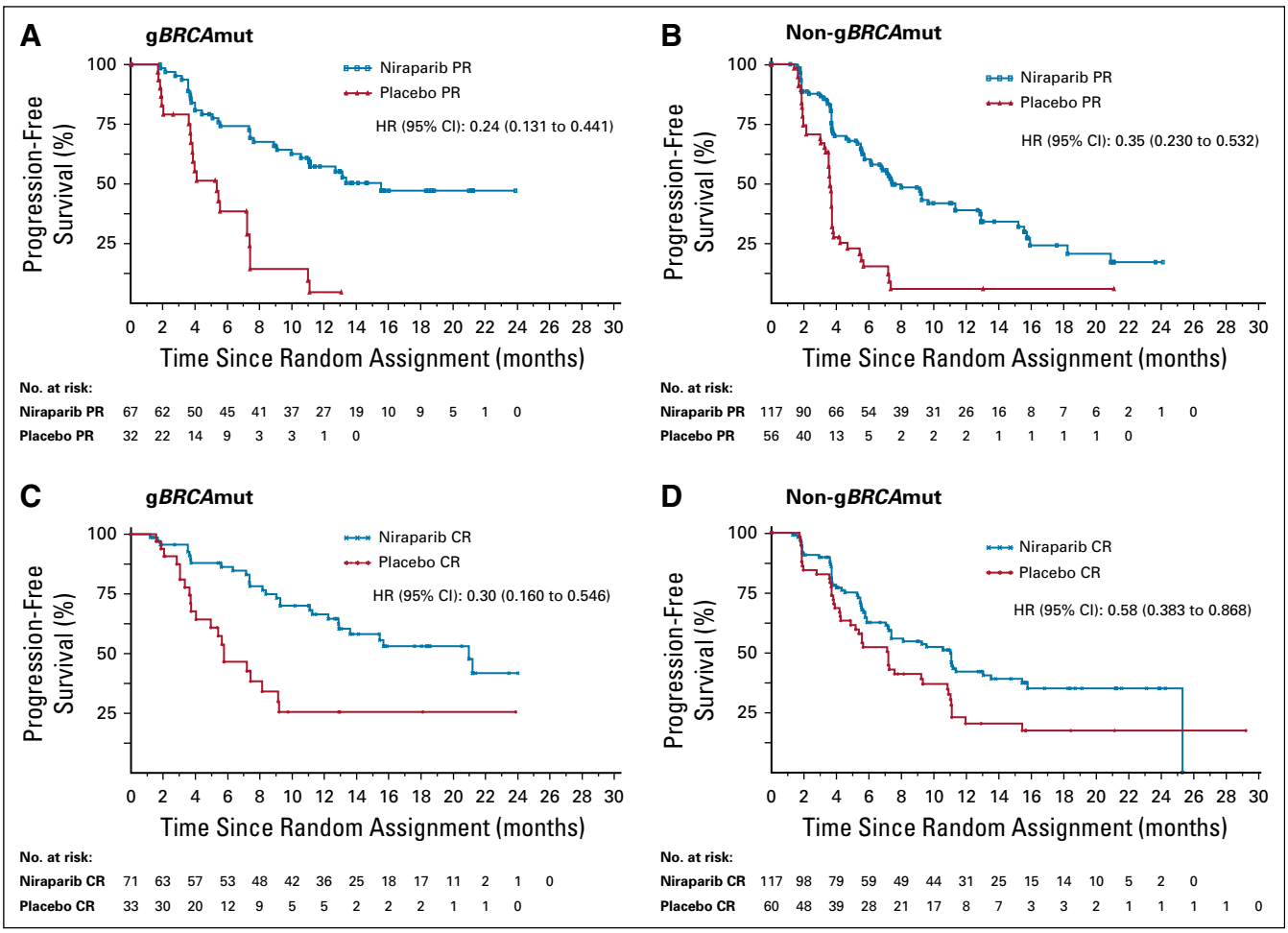

FIG 2. Kaplan-Meier curves for progression-free survival in patients with a partial response (PR) to their last platinum-based therapy in the (A) g*BRCA*mut and (B) non-g*BRCA*mut cohorts, and patients with a complete response (CR) to their last platinum-based therapy in the (C) g*BRCA*mut and (D) non-g*BRCA*mut cohorts. g*BRCA*mut, germline breast cancer susceptibility gene mutation; HR, hazard ratio.

TABLE 2. Grade 3 or Greater AEs That Occurred in at Least 5% of Patients by Response to the Last Platinum-Based Chemotherapy

	No. (%) of Patients					
	Overall		With PR to Last Platinum		With CR to Last Platinum	
AE	Niraparib (n = 367)	Placebo (n = 179)	Niraparib (n = 180)	Placebo (n = 88)	Niraparib (n = 187)	Placebo (n = 91)
Thrombocytopenia	104 (28.3)	1 (0.6)	46 (25.6)	0	58 (31.0)	1 (1.1)
Anemia	91 (24.8)	0	47 (26.1)	0	44 (23.5)	0
Neutropenia	41 (11.2)	1 (0.6)	18 (10.0)	0	23 (12.3)	1 (1.1)
Hypertension	30 (8.2)	4 (2.2)	17 (9.4)	2 (2.3)	13 (7.0)	2 (2.2)
Fatigue	21 (5.7)	0	5 (2.8)	0	16 (8.6)	0

Abbreviations: AE, adverse event; CR, complete response; PR, partial response.

Efficacy

Patients who received niraparib derived a significant clinical benefit relative to placebo regardless of the best response to the last platinum-based therapy (Fig 2). In the g*BRCA*mut cohort, patients with a PR had longer PFS with niraparib compared with placebo (HR, 0.24; 95% CI, 0.131 to 0.441; $P < .0001$). Patients with a CR in the g*BRCA*mut cohort also had longer PFS with niraparib compared with placebo (HR, 0.30; 95% CI, 0.160 to 0.546; $P < .0001$). In the non–g*BRCA*mut cohort, patients with a PR (HR, 0.35; 95% CI, 0.230 to 0.532; $P < .0001$) and patients with a CR (HR, 0.58; 95% CI, 0.383 to 0.868; $P = .0082$) achieved a significant benefit with niraparib treatment compared with placebo.

Safety

Grade 3 or greater AEs that occurred in at least 5% of patients are summarized in Table 2 by response to the last platinum-based therapy. The most common grade 3 or greater AEs among patients with a PR and CR who received niraparib were, respectively, thrombocytopenia (25.6% and 31.0%), anemia (26.1% and 23.5%), neutropenia (10.0% and 12.3%), hypertension (9.4% and 7.0%), and fatigue (2.8% and 8.6%).

Patient-Reported Outcomes

At the screening assessment, there was no observable difference in overall FOSI scores between niraparib and placebo in either of the PR or CR to last platinum-based therapy subgroups. In patients with a CR, the mean overall FOSI score at baseline was 25.3 with niraparib and was 25.5 with placebo; in patients with a PR, the score was 25.3 with niraparib and was 24.9 with placebo. Within each subgroup, no meaningful differences were detected between niraparib and placebo across time with respect to the overall FOSI score (Appendix Table A1, online only). Reports of individual symptoms were similar with niraparib compared with placebo in patients with a PR and with a CR (Appendix Fig A1, online only). Reports of severe symptoms remained low in all groups.

DISCUSSION

In the ENGOT-OV16/NOVA trial, niraparib provided clinical benefit compared with placebo as a maintenance therapy in patients with platinum-sensitive, recurrent ovarian cancer who had a response to their last platinum-based chemotherapy, irrespective of g*BRCA*mut status.[7] Approximately 50% of patients entered the study with a PR to their last platinum-based therapy, which is comparable to rates in other trials of PARP inhibitor maintenance treatment.[6,8] This analysis revealed that patients with a PR to their last platinum therapy who received niraparib experienced a PFS benefit relative to placebo. No additional safety risks were noted for patients with a PR. This suggests that patients with a PR who discontinue after six courses of platinum-based chemotherapy are likely to derive benefit from maintenance treatment with niraparib.

Patient-reported symptoms were comparable between niraparib and placebo at screening and on study regardless of responses to the last platinum-based therapy. For both subgroups, overall mean FOSI scores were similar between treatments. Symptoms such as pain, fatigue, and nausea remained stable or improved with time during the study. The proportion of patients who reported any-grade or severe vomiting remained low. The proportion of patients who experienced other symptoms, such as worry, bloating, and cramps, remained relatively stable throughout the study.

The data presented herein demonstrate that niraparib provides benefit to patients with a PR with a tolerable safety profile and maintained QoL during treatment.[10] Because safety is an important consideration for patients with advanced ovarian cancer, the outcome of this analysis confirms the utility of niraparib maintenance therapy in patients with a PR to their last platinum-based therapy.[4,5]

In summary, our analysis provides evidence to support the use of maintenance therapy with niraparib in patients with a PR to their last platinum-based therapy, because they derive a PFS benefit from niraparib maintenance therapy.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Niraparib Maintenance Therapy in Patients With Recurrent Ovarian Cancer After a Partial Response to the Last Platinum-Based Chemotherapy in the ENGOT-OV16/NOVA Trial

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Leadership: US Oncology
Honoraria: GlaxoSmithKline, Merck, TESARO, Roche, Genentech, AstraZeneca, Gradalis, Advaxis, Amgen, ImmunoGen, Bayer, NuCana BioMed, Insys Therapeutics, Clovis Oncology, Oxigene, Pfizer, Mateon Therapeutics, Precision Oncology, Perthera, Biodesix, AbbVie, Myriad Pharmaceuticals, Incyte, Janssen, Amgen, Genmab, Samumed, Takeda, VBL Therapeutics, Puma Biotechnology, Immunomedics, Conjupro
Consulting or Advisory Role: GlaxoSmithKline, Merck, TESARO, Roche, Genentech, AstraZeneca, Gradalis, Advaxis, Verastem, Cerulean Pharma, Amgen, Vermillion, ImmunoGen, Bayer, NuCana Biomed, Insys Therapeutics, Clovis Oncology, Oxigene, Pfizer, Mateon Therapeutics, Precision Oncology, Perthera, Biodesix, AbbVie, Myriad Pharmaceuticals, Incyte, VBL Therapeutics, Takeda, Samumed
Speakers' Bureau: Roche, Genentech, AstraZeneca, Janssen, Clovis Oncology, TESARO
Research Funding: Novartis (Inst), Amgen (Inst), Genentech (Inst), Lilly (Inst), Janssen (Inst), Array BioPharma (Inst), TESARO (Inst), Morphotek (Inst), Pfizer (Inst), Advaxis (Inst), AstraZeneca (Inst), ImmunoGen (Inst), Regeneron (Inst), NuCana (Inst)

Lucy Gilbert
Honoraria: AstraZeneca, Hoffman-LaRoche, Pfizer
Travel, Accommodations, Expenses: Merck, Pfizer, AstraZeneca

Robert M. Wenham
Stock and Other Ownership Interests: Ovation Diagnostics
Honoraria: TESARO
Consulting or Advisory Role: Mersana, Merck, TESARO, Clovis Oncology, Genentech
Speakers' Bureau: TESARO, Clovis Oncology, Genentech
Research Funding: Merck (Inst), Prescient Therapeutics (Inst)
Travel, Accommodations, Expenses: TapImmune
Other Relationship: AstraZeneca

Benedict Benigno
Speakers' Bureau: AstraZeneca, TESARO, Clovis Oncology
Expert Testimony: Taurig Greenberg

Sujata Arora
Employment: TESARO: A GSK Company

Sebastien J. Hazard
Employment: TESARO: A GSK Company
Stock and Other Ownership Interests: TESARO, ImmunoGen

Mansoor R. Mirza
Leadership: Karyopharm Therapeutics, Sera Prognostics
Stock and Other Ownership Interests: Karyopharm Therapeutics, Sera Prognostics
Honoraria: Roche, Advaxis, AstraZeneca, Cerulean Pharma, Clovis Oncology, Novocure, Pfizer, TESARO
Consulting or Advisory Role: AstraZeneca, Cerulean Pharma, Clovis Oncology, Genmab, Karyopharm Therapeutics, Novocure, Pfizer, TESARO, BioCad, Sotio
Research Funding: AstraZeneca (Inst), Boehringer Ingelheim (Inst), Pfizer (Inst), TESARO (Inst), Clovis Oncology (Inst)
Travel, Accommodations, Expenses: AstraZeneca, Karyopharm Therapeutics, Pfizer, Roche, TESARO, SeraCare

No other potential conflicts of interest were reported.

APPENDIX

TABLE A1. Change From Baseline in FOSI Score

Response to Last Platinum	Cycle	No. of Patients		Niraparib-Placebo LS Mean (95% CI)
		Niraparib	Placebo	
Complete response	2	151	75	−0.7 (−1.76 to 0.35)
	4	137	70	−0.2 (−1.26 to 0.90)
	6	119	56	1.2 (0.02 to 2.33)
	8	99	40	0.2 (−1.11 to 1.47)
	10	87	30	0.9 (−0.52 to 2.33)
	12	78	29	0.4 (−1.08 to 1.86)
	14	63	22	1.1 (−0.45 to 2.74)
Partial response	2	144	77	−0.6 (−1.68 to 0.43)
	4	122	50	0.6 (−0.55 to 1.81)
	6	100	30	0.7 (−0.71 to 2.09)
	8	89	17	1.0 (−0.71 to 2.72)
	10	71	10	−0.1 (−2.22 to 2.06)
	12	69	7	0.7 (−1.77 to 3.16)
	14	57	4	1.7 (−1.42 to 4.83)

NOTE. Obtained from mixed model of the change from baseline with treatment, visit, subgroup, treatment-by-visit, treatment-by-subgroup, and treatment-by-subgroup-by-visit as fixed effects and patient as a random effect.

Abbreviations: FOSI, Functional Assessment of Cancer Therapy–Ovarian Symptom Index; LS, least-squares.

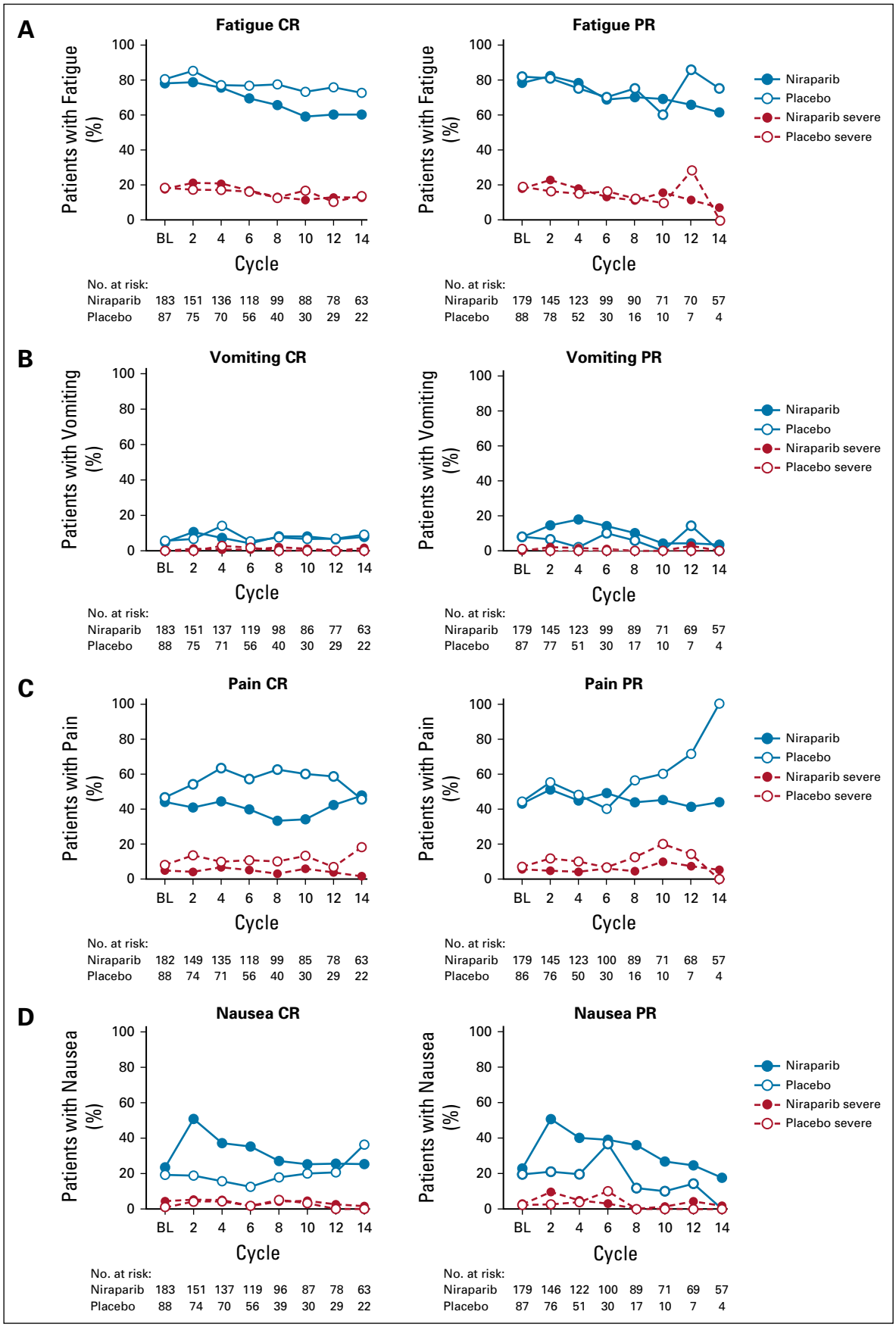

FIG A1. Individual FOSI measures over time by best response to last platinum. BL, baseline; CR, complete response; PR, partial response.

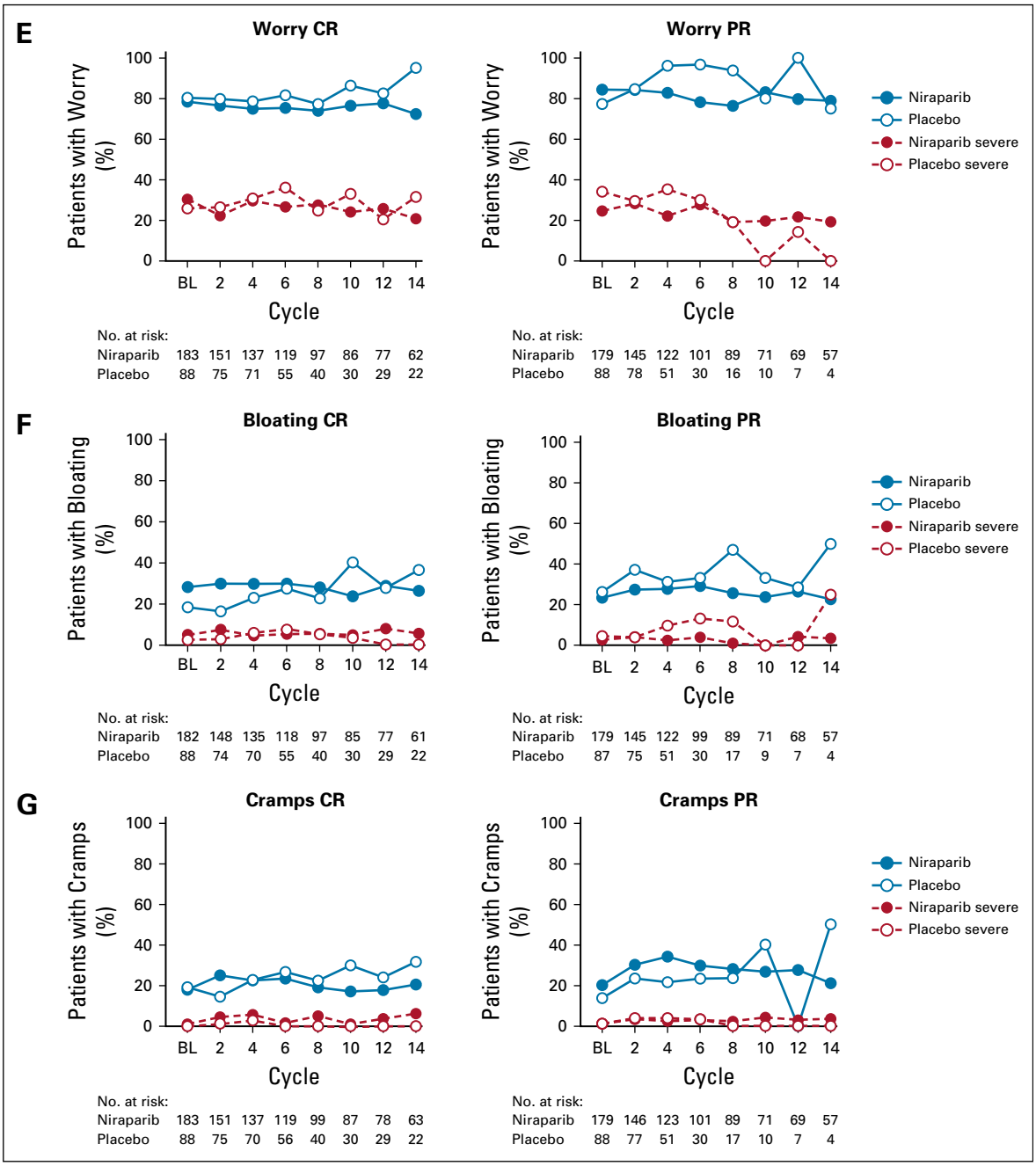

FIG A1. (Continued).